General

Guideline Title

Myocardial infarction with ST-segment elevation. The acute management of myocardial infarction with ST-segment elevation.

Bibliographic Source(s)

National Clinical Guideline Centre. Myocardial infarction with ST-segment elevation. The acute management of myocardial infarction with ST-segment elevation. London (UK): National Institute for Health and Care Excellence (NICE); 2013 Jul. 28 p. (Clinical guideline; no. 167).

Guideline Status

This is the current release of the guideline.

Recommendations

Major Recommendations

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Clinical Guideline Centre (NCGC) on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Note: The wording used in the recommendations in this guideline (for example, words such as 'offer' and 'consider') denotes the certainty with which the recommendation is made (the strength of the recommendations). See the end of the "Major Recommendations" field for further descriptions of the strength of recommendations.

Recommendations

Immediately assess eligibility (irrespective of age, ethnicity, or sex) for coronary reperfusion therapy (either primary percutaneous coronary intervention [PCI] or fibrinolysis) in people with acute ST-elevation myocardial infarction (STEMI).

Do not use level of consciousness after cardiac arrest caused by suspected acute STEMI to determine whether a person is eligible for coronary angiography (with follow-on primary PCI if indicated).

Deliver coronary reperfusion therapy (either primary PCI or fibrinolysis) as quickly as possible for eligible people with acute STEMI.

Offer coronary angiography, with follow-on primary PCI if indicated, as the preferred coronary reperfusion strategy for people with acute STEMI if:

- Presentation is within 12 hours of onset of symptoms and
- Primary PCI can be delivered within 120 minutes of the time when fibrinolysis could have been given.

Offer fibrinolysis to people with acute STEMI presenting within 12 hours of onset of symptoms if primary PCI cannot be delivered within 120 minutes of the time when fibrinolysis could have been given.

When treating people with fibrinolysis, give an antithrombin at the same time.

Offer medical therapy to people with acute STEMI who are ineligible for reperfusion therapy.

Consider coronary angiography, with follow-on primary PCI if indicated, for people with acute STEMI presenting more than 12 hours after the onset of symptoms if there is evidence of continuing myocardial ischaemia.

Do not offer routine glycoprotein IIb/IIIa inhibitors or fibrinolytic drugs before arrival at the catheter laboratory to people with acute STEMI for whom primary PCI is planned.

Offer coronary angiography, with follow-on primary PCI if indicated, to people with acute STEMI and cardiogenic shock who present within 12 hours of the onset of symptoms of STEMI.

Consider coronary angiography, with a view to coronary revascularisation if indicated, for people with acute STEMI who present more than 12 hours after the onset of symptoms and who have cardiogenic shock or go on to develop it.

Offer unfractionated heparin or low molecular weight heparin to people with acute STEMI who are undergoing primary PCI and have been treated with prasugrel or ticagrelor.

Consider thrombus aspiration during primary PCI for people with acute STEMI.

Do not routinely use mechanical thrombus extraction during primary PCI for people with acute STEMI.

Consider radial (in preference to femoral) arterial access for people undergoing coronary angiography (with follow-on primary PCI if indicated).

Offer an electrocardiogram to people treated with fibrinolysis, 60 to 90 minutes after administration. For those who have residual ST-segment elevation suggesting failed coronary reperfusion:

- Offer immediate coronary angiography, with follow-on PCI if indicated.
- Do not repeat fibrinolytic therapy.

If a person has recurrent myocardial ischaemia after fibrinolysis, seek immediate specialist cardiological advice and, if appropriate, offer coronary angiography, with follow-on PCI if indicated.

Consider coronary angiography during the same hospital admission for people who are clinically stable after successful fibrinolysis.

Offer people who have had an acute STEMI written and oral information, advice, support, and treatment on related conditions and secondary prevention (including lifestyle advice), as relevant, in line with published NICE guidance (see Table 1 in the original guideline document).

When commissioning primary PCI services for people with acute STEMI, be aware that outcomes are strongly related to how quickly primary PCI is delivered, and that they can be influenced by the number of procedures carried out by the primary PCI centre.

Recommendations Incorporated from NICE Technology Appraisal Guidance

Ticagrelor in combination with low-dose aspirin is recommended for up to 12 months as a treatment option in people with STEMI – defined as ST elevation or new left bundle branch block on electrocardiogram – that cardiologists intend to treat with primary PCI (this recommendation is adapted from Ticagrelor for the treatment of acute coronary syndromes [NICE technology appraisal guidance 236]).

Bivalirudin in combination with aspirin and clopidogrel is recommended for the treatment of adults with STEMI undergoing primary PCI (this recommendation is from Bivalirudin for the treatment of ST-segment-elevation myocardial infarction [NICE technology appraisal guidance 230]).

Definitions:

Strength of Recommendations

Some recommendations can be made with more certainty than others. The Guideline Development Group (GDG) makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the GDG is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in

the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

Interventions That Must (or Must Not) Be Used

The GDG usually uses 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally 'must' (or 'must not') is used if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions That Should (or Should Not) Be Used – a 'Strong' Recommendation

The GDG uses 'offer' (and similar words such as 'refer' or 'advise') when confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. Similar forms of words (for example, 'Do not offer…') are used when the GDG is confident that an intervention will not be of benefit for most patients.

Interventions That Could Be Used

The GDG uses 'consider' when confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Clinical Algorithm(s)

The following algorithms are provided in the full version of the original guideline document:

- Clinical diagnosis of STEMI
- Time intervals related to each reperfusion strategy

In addition, a National Institute for Health and Care Excellence (NICE) pathway titled "Myocardial Infarction with ST-segment Elevation Overview" is available at the NICE Web site .

Scope

Disease/Condition(s)

Spontaneous onset of ST-segment-elevation myocardial infarction (STEMI) (types 1 and 3 of the 'universal definition of myocardial infarction' categories)

Guideline Category

Diagnosis

Evaluation

Management

Treatment

Clinical Specialty

Cardiology

Critical Care

Emergency Medicine

Family Practice

Internal Medicine

Neurology

Intended Users

Advanced Practice Nurses

Allied Health Personnel

Emergency Medical Technicians/Paramedics

Health Care Providers

Hospitals

Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To offer best practice advice on the care of adults (18 years or older) with spontaneous onset of myocardial infarction with ST-segment elevation (STEMI)

Target Population

- Adults (18 years or older) in the National Health Service in England and Wales believed to be having spontaneous onset of ST-segment-elevation myocardial infarction (STEMI) (types 1 and 3 of the 'universal definition of myocardial infarction' categories)
- Adults in the National Health Service in England and Wales with suggestive symptoms of spontaneous onset of STEMI, but whose electrocardiogram may be difficult to interpret because of the presence of left bundle branch block or permanent pacing
- Where data exist, guidance will address differences between specific populations, such as older adults, women and people from ethnic minorities
- Particular attention will be paid to people with STEMI who remain unconscious following resuscitation

Note: This guideline does not include the following populations or issues:

Children and young people (younger than 18 years)
Patients initially suspected as having STEMI once this diagnosis is excluded (for example, on cardiac catheterisation)
Patients once a diagnosis of STEMI has been excluded (for example, as a complication of coronary revascularisation)
Management of suspected brain injury in those with STEMI who have suffered cardiac arrest
Management of STEMI after hospital discharge, including post-myocardial infarction treatments

Interventions and Practices Considered

1. Patient assessment for eligibility for coronary reperfusion therapy
2. Percutaneous coronary intervention (PCI)
3. Fibrinolysis with an antithrombin
4. Coronary angiography
5. Unfractionated heparin or low-molecular-weight heparin
6. Thrombus aspiration
7. Electrocardiogram
8. Ticagrelor in combination with low-dose aspirin

9. Bivalirudin in combination with aspirin and clopidogrel
10. Specialist consultation

Note: The following were considered but not recommended: routine use of glycoprotein IIb/IIIa inhibitors or fibrinolytic drugs before arrival at the catheter laboratory in people for whom primary PCI is planned, mechanical thrombus extraction during primary PCI.

Major Outcomes Considered

- Major cardiovascular events
- Mortality (all-cause and cardiovascular specific)
- Non-fatal and all (non-fatal and fatal) stroke
- Non-fatal and all (non-fatal and fatal) myocardial reinfarction
- Repeat revascularisation
- Length of hospital stay
- Access site crossover
- Inability to cross the lesion with a wire, balloon or stent during percutaneous coronary intervention (PCI)
- Radiation exposure (X-ray time/fluoroscopic exposure/total radiographic contrast media used/fluoroscopy time)
- Procedure time
- Primary PCI procedural success
- Vascular access site complications
- Quality of life
- Quality-adjusted life year (QALY)
- Intracranial bleeding
- Heart failure
- Major/minor bleeding
- Patient experience (pain)
- Target vessel revascularization
- Contrast-induced nephropathy

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Clinical Guideline Centre (NCGC) on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Developing the Review Questions and Outcomes

Review questions were developed in a PICO framework (patient, intervention, comparison, and outcome) for intervention reviews, and with a framework of population, index tests, reference standard, and target condition for reviews of diagnostic test accuracy. This was to guide the literature searching process and to facilitate the development of recommendations by the Guideline Development Group (GDG). They were drafted by the NCGC technical team and refined and validated by the GDG. The questions were based on the key clinical areas identified in the scope (see Appendix A in the full version of the original guideline document).

A total of 12 review questions (see Section 3 of the full version of the original guideline document) were identified. Full literature searches, critical appraisals, and evidence reviews were completed for all the specified clinical questions.

Searching for Evidence

Clinical Literature Search

Systematic literature searches were undertaken to identify evidence within published literature in order to answer the review questions as per the guidelines manual (2009) (see the "Availability of Companion Documents" field). Clinical databases were searched using relevant medical subject headings, free-text terms, and study type filters where appropriate. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in the English language. All searches were conducted on core databases, MEDLINE, EMBASE, the CINAHL, and The Cochrane Library.

Search strategies were checked by looking at reference lists of relevant key papers, checking search strategies in other systematic reviews and asking GDG for known studies. The questions, the study types applied, the databases searched, and the years covered can be found in Appendix F in the full version of the original guideline document. All searches were updated on 29 November 2012. No papers published after this date were considered.

During the scoping stage, a search was conducted for guidelines and reports on the Web sites listed below and on organisations relevant to the topic. Searching for grey literature or unpublished literature was not undertaken. All references sent by stakeholders were considered.

- Guidelines International Network database (www.g-i-n.net)
- National Guideline Clearinghouse (www.guideline.gov/)
- NICE (www.nice.org.uk)
- National Institutes of Health Consensus Development Program (consensus.nih.gov/)
- National Library for Health (www.library.nhs.uk/)

Health Economic Literature Search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to a ST-segment-elevation myocardial infarction (STEMI) population or terms relating to percutaneous coronary intervention (PCI) or angioplasty in the National Health Service Economic Evaluation Database (NHS EED), the Health Technology Assessment database (HTA), and the Health Economic Evaluations Database (HEED) with no date restrictions. Additionally, the search was run on MEDLINE and EMBASE, with a specific economic filter, from 2010, to ensure recent publications that had not yet been indexed by these databases were identified. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English language.

The search strategies for health economics are included in Appendix F in the full version of the original guideline document. All searches were updated on 29 November 2012. No papers published after this date were considered.

Evidence of Effectiveness

The research fellow:

- Identified potentially relevant studies for each review question from the relevant search results by reviewing titles and abstracts – full papers were then obtained.
- Reviewed full papers against pre-specified inclusion and exclusion criteria to identify studies that addressed the review question in the appropriate population and reported on outcomes of interest (review protocols are included in Appendix C in the full version of the original guideline document).

Inclusion and Exclusion

See the review protocols in Appendix C in the full version of the original guideline document for full details on inclusion and exclusion criteria.

The inclusion and exclusion of studies was based on the review protocols. The GDG were consulted about any uncertainty regarding the inclusion or exclusion of selected studies. The proportion of people with STEMI was among the criteria used for the inclusion of studies in the evidence reviews. Indirect populations were not considered, unless otherwise stated in the evidence reviews. The evidence reviews recorded where there was uncertainty in the definition of the STEMI population.

Review Questions that Include Primary Percutaneous Coronary Intervention (PPCI) as a Comparator

Studies published after 1990 were considered for the majority of the guideline questions in order to ensure that the extracted evidence is reflective of current practice, especially with regard to the widespread adoption of stenting in place of balloon angioplasty for PPCI procedures over the last 15 years. There was no cut-off date for included studies in 2 evidence reviews; use of antithrombin as an adjunct to fibrinolysis (see Chapter 14 in the full version of the original guideline document) and pre-hospital versus in-hospital fibrinolysis (see Chapter 13 of the full version of the original guideline document) as literature published before 1990 was still considered to be relevant by the GDG. The following criteria were also applied for the majority of evidence reviews:

- Where ≥3 randomised controlled trials (RCTs) (with a combined population of ≥500) deploy stents in ≥50% of PPCI procedures (in which stenting is feasible), studies where stents are deployed in <50% of percutaneous coronary intervention (PCI) procedures were excluded.
- Where <3 RCTs deploy stents in ≥50% of PPCI procedures (or the total population of RCTs deploying stents is <500), all studies that began enrolling participants after 1996 were included.
- If <3 RCTs began enrolling participants after 1996 (or the total population is <500), all studies published after 1990 were considered.
- Studies were excluded if <50% of participants had PPCI (that is, population included people who had rescue PCI or facilitated PPCI).

The following exclusion criteria were applied for the facilitated primary percutaneous coronary intervention evidence review:

- RCTs that did not use stents or <50% people received stents
- RCTs that did not mention the percentage of stent usage

Review Questions That Include Fibrinolytic Agents as a Comparator

The search strategy reflected NICE technology appraisal 52 , which recommends alteplase, reteplase, streptokinase, and tenecteplase for in-hospital fibrinolysis and reteplase and tenecteplase for pre-hospital fibrinolysis.

Review Questions and Number of Participants in Studies

No limits were applied for study sample size except for the evidence reviews of culprit versus complete revascularisation, hospital volumes of primary percutaneous coronary intervention, time to reperfusion, and facilitated primary percutaneous coronary intervention. For the evidence review of culprit versus complete revascularisation, cohort studies ≥500 participants were included. For the evidence review of hospital volumes of primary percutaneous coronary intervention, prospective and retrospective observational studies with >1000 participants were included. The time to reperfusion review only included registry studies if there were >100,000 participants unless they were conducted in the UK. Studies that performed meta-regression analyses of RCT evidence were only selected if ≥10 RCTs were included in the analyses, as per standard review methodology that for meta-regression studies there should be at least 10 trials per covariate. For the evidence review of facilitated primary percutaneous coronary intervention, studies with <60 participants were excluded if there were larger RCTs.

Evidence of Cost-effectiveness

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts – full papers were then obtained.
- Reviewed full papers against pre-specified inclusion and exclusion criteria to identify relevant studies (see below for details)

Inclusion and Exclusion

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost–effectiveness, cost–benefit, and cost–consequence analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially includable as economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost effectiveness without disaggregated costs and effects, were excluded. Abstracts, posters, reviews, letters, editorials, comment articles, publications not in English, and unpublished studies were excluded. Studies judged to have an applicability rating of 'not applicable' were excluded (this included studies that took the perspective of a non-Organisation for Economic Co-operation and Development [OECD] country).

The remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high-quality, directly applicable UK analysis was available other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section in the full version of the original guideline document.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist (the Guidelines Manual

[see the "Availability of Companion Documents" field]) and the health economics research protocol in Appendix C in the full version of the original guideline document.

Number of Source Documents

The number of studies identified for each clinical question is provided in Appendix D in the full version of the original guideline document (see the "Availability of Companion Documents" field).

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Overall Quality of Outcome Evidence in Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Level	Description
High	Further research is very unlikely to change confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
Very Low	Any estimate of effect is very uncertain.

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Clinical Guideline Centre (NCGC) on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

Evidence of Effectiveness

The research fellow:

- Critically appraised relevant studies using the appropriate checklist as specified in the Guidelines Manual (see the "Availability of Companion Documents" field)
- Extracted key information about the study's methods and results into evidence tables (evidence tables are included in Appendix G in the full version of the original guideline document)
- Generated summaries of the evidence by outcome (included in the relevant chapter write-ups in the full version of the original guideline document):
    - Randomised studies: meta-analysed, where appropriate, and reported in Grading of Recommendations Assessment, Development and Evaluation (GRADE) profiles (for clinical studies)
    - Observational studies: data presented as a range of values in GRADE profiles

Methods of Combining Clinical Studies

Data Synthesis for Intervention Reviews

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for the binary outcomes: mortality (all-cause and cardiovascular specific), non-fatal and all (fatal and non-fatal) stroke, intracranial bleeding, non-fatal and all (fatal and non-fatal) myocardial reinfarction, heart failure, repeat revascularisation, major bleeding, minor bleeding, primary percutaneous coronary intervention (PPCI) vascular access site complications, renal failure, refractory ischaemia, and neurologically intact survival (Cerebral Performance Categories [CPC] score). Repeat revascularisation was assumed to be target vessel revascularisation and definitions were reported in the evidence reviews where given. The continuous outcomes of hospital stay, total fluoroscopy contrast media used during PPCI, PPCI fluoroscopy time, PPCI access site crossover, PPCI procedure length, use of intra-aortic balloon pump, and quality of life were analysed using an inverse variance method for pooling weighted mean differences and where the studies had different scales, standardised mean differences were used. Where reported, time-to-event data was presented as a hazard ratio.

Data Synthesis of Outcomes and Study Follow-up

Each outcome was analysed at short-term and longer-term follow-up. The majority of questions used a short-term follow-up defined as intervals ≤30 days (the included studies table for each evidence review specifies the exact time point). The reported outcome interval closest to 30 days was analysed where more than 1 interval was reported. The rescue percutaneous coronary intervention and the routine early angiography evidence reviews analysed short-term outcomes at multiple time intervals, namely in-hospital, 30 days and 6 weeks. Longer-term follow-up was defined as intervals >6 weeks. When multiple time intervals >6 weeks were reported, the value as close to 6 months as possible was used (the exact duration is specified in the included studies table for each review and the forest plots). Six months was chosen for consistency and because outcome rates were substantially reduced and largely constant by this stage, while confidence in the accuracy of outcomes recorded at longer follow-up intervals may be unduly affected by large numbers of participants lost to follow-up.

Where possible, follow-up data (recorded after >6 weeks) was also analysed as 'time-to-event' using the longest available follow-up data. This analysis replaced longer-term follow-up data analysed as relative risk, but only when this did not result in the exclusion of data from studies that could only be analysed as relative risk, in which case data was analysed as both relative risk and time-to-event.

In terms of decision-making, the Guideline Development Group gave greater weighting to longer-term data because it demonstrated whether effects were sustained or not. Short-term data was also reviewed because many studies only recorded follow-up at 30 days and short-term data provides results that can be more readily attributed to the investigated interventions.

Data Synthesis and Population Subgroups

The following groups were considered separately if data were present:

- People with diabetes
- People from ethnic minorities
- People with renal dysfunction
- Females
- People aged over 70 years (if data was available, a cut off of those aged over 65 years was considered instead)

Sub-analyses based on these groups were conducted where there was sufficient data available and if the subgroup was defined a priori. If there was insufficient data for analyses relevant data was reported in the evidence tables or in summary table in the evidence reviews.

Statistical heterogeneity was assessed by considering the chi-squared test for significance at $p<0.1$ or an I-squared inconsistency statistic of >50% to indicate significant heterogeneity. Sensitivity analysis based on the quality of studies was also carried out if there were differences, with particular attention paid to allocation concealment, blinding, and loss to follow-up (missing data). In cases where there was inadequate allocation concealment, unclear blinding, more than 50% missing data, or differential missing data, this was examined in a sensitivity analysis. For the latter, the duration of follow-up was also taken into consideration prior to including in a sensitivity analysis. The following were predefined subgroups for sensitivity analysis for all evidence reviews: ethnic minorities, people with diabetes, people with renal dysfunction, females, and people aged over 70 years. For the evidence reviews of facilitated primary percutaneous coronary intervention, rescue percutaneous coronary intervention, hospital volumes of primary percutaneous coronary intervention and unconscious people, the following were additional predefined subgroups; people receiving balloon angioplasty versus stenting, and people receiving glycoprotein IIb/IIIa inhibitors (GPIs) with percutaneous coronary intervention (PCI) versus no GPIs with PCI. The routine angiography evidence review had the following additional predefined subgroups: high risk versus low

risk people, mean time interval to angiography after fibrinolysis, and people receiving balloon angioplasty versus stenting. The femoral versus radial approach for primary percutaneous coronary intervention evidence review had the following additional predefined subgroups: operator expertise, people receiving GPIs versus people not receiving GPIs, and people receiving GPIs with PCI versus no GPIs with PCI, and stent usage. The culprit versus complete revascularisation evidence review had the following additional predefined subgroups: stent usage and GPI therapy.

Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. If no sensitivity analysis was found to completely resolve statistical heterogeneity then a random-effects (DerSimonian and Laird) model was employed to provide a more conservative estimate of the effect.

The means and standard deviations of continuous outcomes were required for meta-analysis. However, in cases where standard deviations were not reported, the standard error was calculated if the p values or 95% confidence intervals were reported and meta-analysis was undertaken with the mean and standard error using the generic inverse variance method in Cochrane Review Manager (RevMan5) software (http://ims.cochrane.org/revman). Where p values were reported as 'less than', a conservative approach was undertaken. For example, if p value was reported as '$p \leq 0.001$', the calculations for standard deviations will be based on a p value of 0.001. If these statistical measures were not available then the methods described in Section 16.1.3 of the Cochrane Handbook (September 2009) 'missing standard deviations' were applied as the last resort.

For binary outcomes, absolute event rates were also calculated using the GRADEpro software using event rate in the control arm of the pooled results.

Appraising the Quality of Evidence by Outcomes

The evidence for outcomes from the included randomised controlled trials (RCTs) and observational studies were evaluated and presented using an adaptation of the 'GRADE toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software (GRADEpro) developed by the GRADE working group was used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 'Clinical evidence profile' table, reported in this guideline, includes details of the quality assessment pooled outcome data, where appropriate, an absolute measure of intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate the sum of the sample size for continuous outcomes. For binary outcomes such as number of people with an adverse event, the event rates (n/N: number of people with events divided by sum of number of people) are shown with percentages. Reporting or publication bias was only taken into consideration in the quality assessment and included in the clinical evidence profile table if it was apparent. Each outcome was examined separately for the quality elements listed and each graded using the quality levels listed in Table 2 of the full version of the original guideline document. The main criteria considered in the rating of these elements are discussed below. Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome listed in the "Rating Scheme for the Strength of the Evidence" field.

Grading the Quality of Clinical Evidence for RCTs and Observational Studies

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

1. A quality rating was assigned, based on the study design. RCTs start HIGH and observational studies as LOW, uncontrolled case series as LOW or VERY LOW.
2. The rating was then downgraded for the specified criteria: Study limitations, inconsistency, indirectness, imprecision, and reporting bias. Observational studies were upgraded if there was: a large magnitude of effect, dose-response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have 'serious' or 'very serious' risk of bias was rated down −1 or −2 points respectively.
3. The downgraded and upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as HIGH and the overall quality became MODERATE, LOW, or VERY LOW if 1, 2, or 3 points were deducted respectively.
4. The reasons or criteria used for downgrading were specified in the footnotes to the recommendations.

The details of criteria used for each of the main quality elements (study limitations, inconsistency, indirectness, and imprecision) are discussed further in Sections 3.3.5 to 3.3.8 of the full version of the original guideline document.

Grading the Quality of Clinical Evidence of Studies for Meta-regression Analyses of RCTs Evidence

The time to reperfusion (delay between fibrinolysis and primary percutaneous coronary intervention) evidence review used meta-regression analyses of data from RCTs or registries. The quality of evidence for these types of studies is largely dependent upon the following: the models

used to analyse the data (simple linear regression versus more complex modelling) and the type and number of studies included in the model (RCT evidence from individual patient data or study-level and registry data).

The GDG considered that individual patient data (IPD) was the most robust quality evidence versus study-level data and registry data. The original data for each participant in an included study is used in meta-analysis or in this evidence review in meta-regression analysis. IPD reduces the risk of outcome reporting bias and the reasons for missing outcome data can be identified. Outcomes in meta-regression analyses that used study-level data, which is subject to ecological fallacy, were downgraded. Ecological fallacy assumes that individual members of a group have the average characteristics of the group as a whole. Statistics that use group characteristics do not necessarily apply to individuals within the group, and do not account for the fact that individuals have a greater variability than the variability of their mean. The NCGC technical team also downgraded outcomes that were derived from fewer than 10 RCTs and from older RCTs where included RCT evidence may not reflect current clinical practice (for example stent usage and GPI IIb/IIIa inhibitor therapy). Outcomes from registry studies were downgraded because the data was derived from non-randomised participants. Outcomes data from simple linear regression models were also considered to less robust evidence compared to models that performed sensitivity analyses.

Evidence Statements

Evidence statements were formed for each outcome indicating the quantity and quality of evidence available, and the outcome and population to which they relate.

Evidence of Cost-effectiveness

Literature Review

The health economist:

- Critically appraised relevant studies using the economic evaluations checklist as specified in the guidelines manual.
- Extracted key information about the studies' methods and results into evidence tables (evidence tables are included in Appendix H in the full version of the original guideline document).
- Generated summaries of the evidence in National Institute for Health and Care Excellence (NICE) economic evidence profiles (included in the relevant chapter for each review question in the full version of the original guideline document) – see below for details.

NICE Economic Evidence Profiles

The NICE economic evidence profile has been used to summarise cost and cost-effectiveness estimates. The economic evidence profile shows an assessment of applicability and methodological quality for each economic study, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from the Guidelines Manual (see the "Availability of Companion Documents" field). It also shows incremental costs, incremental effects (for example, quality-adjusted life-years [QALYs]) and the incremental cost-effectiveness ratio from the primary analysis, as well as information about the assessment of uncertainty in the analysis.

If a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Note from the National Guideline Clearinghouse (NGC): This guideline was developed by the National Clinical Guideline Centre (NCGC) on behalf of the National Institute for Health and Care Excellence (NICE). See the "Availability of Companion Documents" field for the full version of this guidance.

This guidance was developed in accordance with the methods outlined in the NICE Guidelines Manual 2009 (see the "Availability of Companion Documents" field).

A multidisciplinary Guideline Development Group (GDG) comprising professional group members and consumer representatives of the main stakeholders developed this guideline. The group met every 6 weeks during the development of the guideline.

Developing Recommendations

Over the course of the guideline development process, the GDG was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in Appendices G and H in the full version of the original guideline document.
- Summary of clinical and economic evidence and quality (as presented in Chapters 5 to 17 in the full version of the original guideline document)
- Forest plots (see Appendix I in the full version of the original guideline document)
- A description of the methods and results of the comparative cost analyses undertaken for the guideline (see Appendices L and M in the full version of the original guideline document)

Recommendations were drafted on the basis of the GDG interpretation of the available evidence, taking into account the balance of benefits, harms, and costs. When clinical and economic evidence was of poor quality, conflicting, or absent, the GDG drafted recommendations based on their expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, economic costs or implications compared to the benefits, current practices, recommendations made in other relevant guidelines, patient preferences, and equality issues. The consensus recommendations were agreed through discussions in the GDG. The GDG also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation.

The main considerations specific to each recommendation are outlined in the 'Recommendations and Link to Evidence' sections within each chapter in the full version of the original guideline document.

Rating Scheme for the Strength of the Recommendations

Strength of Recommendations

Some recommendations can be made with more certainty than others. The Guideline Development Group (GDG) makes a recommendation based on the trade-off between the benefits and harms of an intervention, taking into account the quality of the underpinning evidence. For some interventions, the GDG is confident that, given the information it has looked at, most patients would choose the intervention. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the strength of the recommendation).

Interventions That Must (or Must Not) Be Used

The GDG usually uses 'must' or 'must not' only if there is a legal duty to apply the recommendation. Occasionally 'must' (or 'must not') is used if the consequences of not following the recommendation could be extremely serious or potentially life threatening.

Interventions That Should (or Should Not) Be Used – a 'Strong' Recommendation

The GDG uses 'offer' (and similar words such as 'refer' or 'advise') when confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. Similar forms of words (for example, 'Do not offer…') are used when the GDG is confident that an intervention will not be of benefit for most patients.

Interventions That Could Be Used

The GDG uses 'consider' when confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient's values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Cost Analysis

Undertaking New Health Economic Analysis

As well as reviewing the published economic literature for each review question, as described above, new economic analysis was undertaken by the health economist in selected areas. Priority areas for new health economic analysis were agreed by the Guideline Development Group (GDG) after formation of the review questions and consideration of the available health economic evidence.

The GDG did not identify any priority areas which were suitable for original economic modelling. The GDG identified radial versus femoral access

primary percutaneous coronary intervention (PPCI) and the use of thrombus extraction devices as the two highest priority areas for original comparative cost analysis. These were chosen as in each case both options (PPCI via radial access or femoral access; PPCI with and without the use of thrombus extraction devices) are in common use, their relative cost effectiveness was uncertain, and their relative costs were not known but thought to be similar.

The following general principles were adhered to in developing the comparative cost analyses:

- Methods were consistent with the NICE reference case.
- The GDG was consulted during the research and interpretation of the analyses.
- Data inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible.
- When published data was not available GDG expert opinion was used.
- Data inputs and assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis where appropriate and limitations were discussed.
- The analyses were peer-reviewed by an independent external health economist.

Full methods for the comparative cost analyses are described in Appendices L and M in the full version of the original guideline document.

Cost-effectiveness Criteria

In general, an intervention was considered to be cost-effective if either of the following criteria applied (given that the estimate was considered plausible):

a. The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
b. The intervention cost less than £20,000 per quality-adjusted life-year (QALY) gained compared with the next best strategy.

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'from evidence to recommendations' section of the relevant chapter with reference to issues regarding the plausibility of the estimate or to the factors set out in the National Institute for Health and Care Excellence (NICE) report 'Social value judgements: principles for the development of NICE guidance'.

If a study reported the cost per life year gained but not QALYs, the cost per QALY gained was estimated by multiplying by an appropriate utility estimate to aid interpretation. The estimated cost per QALY gained is reported in the economic evidence profile with a footnote detailing the life-years gained and the utility value used. When QALYs or life years gained are not used in the analysis, results are difficult to interpret unless one strategy dominates the others with respect to every relevant health outcome and cost.

See the individual chapters of the full version of the original guideline document (see the "Availability of Companion Documents" field) for discussions of the cost-effectiveness of specific recommendations.

In the Absence of Cost-effectiveness Evidence

When no relevant published studies were found, and a new analysis was not prioritised, the GDG made a qualitative judgement about cost-effectiveness by considering expected differences in resource use between options and relevant UK National Health Service unit costs alongside the results of the clinical review of effectiveness evidence.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

This guidance is subject to a 6-week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE Web site when the pre-publication check of the full guideline occurs.

The final draft was submitted to the Guideline Review Panel for review prior to publication.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate acute management of myocardial infarction with ST-segment elevation

See the "Trade-off between clinical benefits and harms" section in the full version of the original guideline document (see the "Availability of Companion Documents" field) for additional details about benefits of specific interventions.

Potential Harms

Fibrinolysis

- Fibrinolysis can be administered early in the treatment pathway by intravenous injection (either in the pre-hospital setting or in the emergency department of a hospital). In these circumstances fibrinolysis is given on the basis of a clinical assessment and the presence of ST-segment elevation on a 12-lead electrocardiogram, but without angiographic confirmation of thrombotic coronary artery occlusion. Hence there is a risk that fibrinolysis may be administered inappropriately to people who have other causes of chest pain or ST-segment elevation (for example aortic dissection, apical ballooning syndrome, pericarditis, oesophagitis).
- Fibrinolysis is associated with a risk of bleeding and up to 13% of people require blood transfusion. In addition intracranial bleeding occurs in around 1% of people within 24 hours of treatment and most of these people will die or be left with major disability. Although the benefit of fibrinolysis is critically dependent on the delay to treatment, the risk of haemorrhagic stroke is not influenced by treatment delay, but is increased by female gender, advanced age, low body weight, blood pressure, and previous cerebrovascular disease.
- In the STREAM (Strategic Reperfusion Early After Myocardial Infarction) trial, fibrinolysis was associated with a significant excess risk of haemorrhagic stroke that required a protocol amendment (reduction in the dose of fibrinolytic in people 75 years of age or older) during the trial.
- There is convincing evidence that fibrinolysis (in comparison to primary percutaneous coronary intervention [PPCI]) is associated with a higher risk of haemorrhagic stroke, reinfarction, and bleeding.
- Pre-hospital fibrinolysis was associated with a significant increase in the combined rate of major and minor bleeding but no evidence was available for intracranial bleeding.

Rescue Percutaneous Coronary Intervention (PCI)

Rescue PCI increased the incidence of minor bleeding. The available data do not allow meaningful conclusions regarding heart failure, stroke, and major bleeding.

Antithrombotic Drugs

- Multiple different possible combinations of antithrombotic drugs are used in patients who are undergoing PPCI. The relative efficacy and safety (especially bleeding risk) of these different combinations are influenced by the pharmacology, dosing, and timing of administration of the different agents.
- In the PLATO (ticagrelor) and TRITON TIMI 38 (prasugrel) trials the majority of participants, including patients undergoing PPCI, were treated with unfractionated heparin or low molecular weight heparin. In both trials treatment with ticagrelor or prasugrel (versus clopidogrel) was associated with a reduction in cardiovascular event rates but an increased risk of bleeding.

See the "Trade-off between clinical benefits and harms" section in the full version of the original guideline document (see the "Availability of Companion Documents" field) for additional details about harms of specific interventions.

Contraindications

Contraindications

Fibrinolysis may be contraindicated in around 25% of people with evolving ST-segment elevation myocardial infarction (STEMI) because of bleeding risk or comorbidity.

Qualifying Statements

Qualifying Statements

- This guidance represents the view of the National Institute for Health and Care Excellence (NICE), which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer, and informed by the summaries of product characteristics of any drugs.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.
- Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If someone does not have the capacity to make decisions, healthcare professionals should follow the Department of Health's advice on consent , the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards. In Wales, healthcare professionals should follow advice on consent from the Welsh Government.
- For all recommendations, NICE expects that there is discussion with the patient about the risks and benefits of the interventions, and their values and preferences. This discussion aims to help them to reach a fully informed decision.
- The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

Implementation of the Guideline

Description of Implementation Strategy

The National Institute for Health and Care Excellence (NICE) has developed tools to help organisations implement this guidance. These are available on the NICE Web site (see also the "Availability of Companion Documents" field).

Key Priorities for Implementation

The following recommendations have been identified as priorities for implementation.

- Immediately assess eligibility (irrespective of age, ethnicity, or sex) for coronary reperfusion therapy (either primary percutaneous coronary intervention [PCI] or fibrinolysis) in people with acute ST-elevation myocardial infarction (STEMI).
- Do not use level of consciousness after cardiac arrest caused by suspected acute STEMI to determine whether a person is eligible for coronary angiography (with follow-on primary PCI if indicated).
- Deliver coronary reperfusion therapy (either primary PCI or fibrinolysis) as quickly as possible for eligible people with acute STEMI.
- Offer coronary angiography, with follow-on primary PCI if indicated, as the preferred coronary reperfusion strategy for people with acute STEMI if:
    - Presentation is within 12 hours of onset of symptoms and
    - Primary PCI can be delivered within 120 minutes of the time when fibrinolysis could have been given.

- Offer fibrinolysis to people with acute STEMI presenting within 12 hours of onset of symptoms if primary PCI cannot be delivered within 120 minutes of the time when fibrinolysis could have been given.
- Consider coronary angiography, with follow-on primary PCI if indicated, for people with acute STEMI presenting more than 12 hours after the onset of symptoms if there is evidence of continuing myocardial ischaemia.
- Offer coronary angiography, with follow-on primary PCI if indicated, to people with acute STEMI and cardiogenic shock who present within 12 hours of the onset of symptoms of STEMI.
- Offer an electrocardiogram to people treated with fibrinolysis, 60 to 90 minutes after administration. For those who have residual ST-segment elevation suggesting failed coronary reperfusion:
  - Offer immediate coronary angiography, with follow-on PCI if indicated.
  - Do not repeat fibrinolytic therapy.
- If a person has recurrent myocardial ischaemia after fibrinolysis, seek immediate specialist cardiological advice and, if appropriate, offer coronary angiography, with follow-on PCI if indicated.
- When commissioning primary PCI services for people with acute STEMI, be aware that outcomes are strongly related to how quickly primary PCI is delivered, and that they can be influenced by the number of procedures carried out by the primary PCI centre.

Implementation Tools

Audit Criteria/Indicators

Clinical Algorithm

Foreign Language Translations

Mobile Device Resources

Patient Resources

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Staying Healthy

IOM Domain

Effectiveness

Patient-centeredness

Timeliness

Identifying Information and Availability

Bibliographic Source(s)

National Clinical Guideline Centre. Myocardial infarction with ST-segment elevation. The acute management of myocardial infarction with ST-segment elevation. London (UK): National Institute for Health and Care Excellence (NICE); 2013 Jul. 28 p. (Clinical guideline; no. 167).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

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Guideline Developer(s)

National Clinical Guideline Centre - National Government Agency [Non-U.S.]

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Guideline Committee

Guideline Development Group

Composition of Group That Authored the Guideline

Guideline Development Group Members: Sotiris Antoniou, Consultant Pharmacist, Barts Health NHS Trust; Charles Deakin, Consultant in Cardiac Anaesthesia and Intensive Care, University Hospital Southampton; Huon Gray (*Chair*), Consultant Cardiologist, Wessex Cardiac Unit, University of Southampton Hospital NHS Foundation Trust; Rob Henderson (*Deputy Chair*), Consultant Cardiologist, Nottingham University Hospitals NHS Trust; Jason Kendall, Consultant in Emergency Medicine, Frenchay Hospital, North Bristol NHS Trust; Hugh McIntyre, Consultant Physician, East Sussex Hospitals Trust; Jim McLenachan, Consultant Cardiologist, Leeds General Infirmary; Francesco Palma, Patient and carer member; Gerald Robinson, Patient and carer member; Fiona Sayers, Head of Nursing, Cardiology and Acute Services, Frimley Park Hospital; Dave Smith, Consultant Interventional Cardiologist, Regional Cardiac Centre, Morriston Hospital; David Smith, Consultant Cardiologist, Royal Devon and Exeter NHS Hospital Trust; Mark Vaughan, GP, Llanelli; Mark Whitbread, Senior Paramedic, London Ambulance Service, Essex

Financial Disclosures/Conflicts of Interest

At the start of the guideline development process all Guideline Development Group (GDG) members declared interests including consultancies, fee-paid work, shareholdings, fellowships, and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest. Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix B in the full version of the original guideline document (see the "Availability of Companion Documents" field).

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site. Also available for download as a Kindle or EPUB ebook from the NICE Web site.

Availability of Companion Documents

The following are available:

- Myocardial infarction with ST-segment elevation. Full guideline. London (UK): National Institute for Health and Care Excellence (NICE); 2013 Jul. 310 p. (Clinical guideline; no 167). Electronic copies: Available in Portable Document Format (PDF) from the National Institute for Health and Care Excellence (NICE) Web site.
- Myocardial infarction with ST-segment elevation. Appendices A-H. London (UK): National Institute for Health and Care Excellence (NICE); 2013 Jul. 407 p. (Clinical guideline; no 167). Electronic copies: Available in PDF from the NICE Web site.
- Myocardial infarction with ST-segment elevation. Appendices I-P. London (UK): National Institute for Health and Care Excellence (NICE); 2013 Jul. 216 p. (Clinical guideline; no 167). Electronic copies: Available in PDF from the NICE Web site.
- Myocardial infarction with ST-segment elevation. Baseline assessment tool. London (UK): National Institute for Health and Care Excellence (NICE); 2013 Jul. (Clinical guideline; no 167). Electronic copies: Available from the NICE Web site.
- Myocardial infarction with ST-segment elevation. Clinical audit tool. London (UK): National Institute for Health and Care Excellence (NICE); 2013 Jul. (Clinical guideline; no 167). Electronic copies: Available from the NICE Web site.
- Myocardial infarction with ST-segment elevation. Costing report. London (UK): National Institute for Health and Care Excellence (NICE); 2013 Jul. 26 p. (Clinical guideline; no 167). Electronic copies: Available in PDF from the NICE Web site.
- Myocardial infarction with ST-segment elevation. Costing template. London (UK): National Institute for Health and Care Excellence (NICE); 2013 Jul. (Clinical guideline; no 167). Electronic copies: Available from the NICE Web site.
- Myocardial infarction with ST-segment elevation overview. NICE pathway. London (UK): National Institute for Health and Care Excellence (NICE). Electronic copies: Available from the NICE Web site.
- The guidelines manual 2009. London (UK): National Institute for Health and Care Excellence (NICE); 2009 Jan. Electronic copies: Available in PDF from the NICE Archive Web site.

Patient Resources

The following is available:

- Emergency assessment and treatment for a heart attack. Information for the public. London (UK): National Institute for Health and Care Excellence (NICE); 2013 Jul. Electronic copies: Available from the National Institute for Health and Care Excellence (NICE) Web site. Also available for download as a Kindle or EPUB ebook from the NICE Web site. Also available in Welsh from the NICE Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

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